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[0005] Synchronous luminescence (SL) methodology is an improved technology over LIF and provides a way to measure the luminescence signal and spectral fingerprints for rapid screening of complex chemical samples. The general theory of the SL method has been described previously in "Synchronous Excitation Spectroscopy," authored by the inventor of the present application T. Vo-Dinh, in Modern Fluorescence Spectroscopy, Chapter 5, Ed. by E. L. Wehry (Plenum Publ. Corp. 1981), which is incorporated herein by reference in its entirety. *In contrast to SL, conventional luminescence spectroscopy uses either a fixed-wavelength excitation (λ_{ex}) to produce an emission spectrum or a fixed wavelength emission (λ_{em}) to record an excitation spectrum. With SL, the luminescence signal is recorded while both λ_{em} and λ_{ex} are simultaneously scanned.* A constant wavelength interval is generally maintained between the excitation and the emission monochromators throughout the spectrum. As a result, the observed intensity I_s of the synchronous signal can be written as a product of two functions as follows:

$$I_s (\lambda_{ex}, \lambda_{em}) = k\, c\, E_x (\lambda_{ex}) \cdot E_M (\lambda_{ex}) \qquad (1)$$

where:

k = a constant,
c = concentration of the analyte,
E_λ = excitation function, and
E_M = emission function

[0006] For a single molecular species the observed intensity I_S is simplified often to a single peak, and the bandwidth is narrower than for the conventional emission spectrum. Since the SL spectrum of each component becomes sharper due to the band-narrowing effect of the SL technique, the resulting fluorescence spectrum of the tissues sample becomes better resolved with a plurality of readily identifiable sharp individual emission peaks.

The associated system claimed in claim 15 includes "structure for synchronously scanning a wavelength of said excitation radiation and a wavelength of said emission radiation". Claim 21 recites a preferred embodiment of the "structure for synchronously scanning a wavelength of said excitation radiation" by reciting "said excitation radiation source is a broadband source, structure for synchronously scanning comprising a first acousto-optic tunable filter (AOTF) having a variable input radio frequency selected to achieve a range of excitation wavelengths". Similarly, claim 22 recites "wherein structure for synchronously scanning further comprises a second acousto-optic tunable filter (AOTF) having a variable input radio frequency selected to achieve a range of emission wavelengths. Applicant's paragraphs 45 and 46 with reference to Fig. 3 describe a system

according to the invention 300 including a broadband light source with two (2) AOTFs to implement the claimed synchronous scanning.

Accordingly, a key point is that the claimed synchronous scanning requires scanning of the excitation wavelength, which necessitates a broadband excitation source and a structure for scanning through the broadband spectrum, as well as a structure for scanning the emission wavelengths which reach the detector.

The measurements provided by Applicant's claimed synchronous luminescent system are also distinct from those provided by conventional luminescent systems. Specifically, when the radiation source is configured to emit excitation radiation at a plurality of different wavelengths and the radiation detector is configured to synchronously scan radiation emitted by the target with the excitation radiation, an excitation-emission map results, in which the excitation-emission pairs for fluorescence are represented in a three dimensional array with the X and Y axes representing excitation and emission wavelengths respectively with the Z axis corresponding to the fluorescence intensity returned at excitation wavelength X and emission wavelength Y.

Regarding Clark, the Examiner asserts:

Clarke anticipates all claimed features in claims 1-26.

Claims 1, 15, and 26: Clarke discloses a method and system of diagnosis using excitation radiation through a single optical waveguide or a single optical wavelength bundle where a region of interest or target tissue of the excitation radiation emits emission radiation in response, receiving the emission radiation with co-registration of the excitation and emission radiations and synchronously scanning a wavelength of excitation-emission radiations to obtain a spectrum (column 2, lines 27-63; column 6, lines 35-55; column 8, lines 10-32).

Applicant respectfully disagrees with the Examiner's assertions regarding Clarke, but needs to point out an error in the above assertions first. The assertion above includes "synchronous scanning a wavelength of *excitation emission radiations* to obtain a spectrum". However, synchronous scanning requires scanning of both the excitation and the emission wavelength. Applicant will assume the Examiner meant scanning a wavelength of both the excitation and emission wavelength above, and will demonstrate that Clarke does not disclose or suggest scanning either. Accordingly, as will be demonstrated below, Clarke doers not disclose or suggest the "synchronous scanning" recited in method claim 1 and the implicitly asserted "structure for synchronously scanning a wavelength of said excitation radiation and a wavelength of said emission radiation" recited in system claim 15.

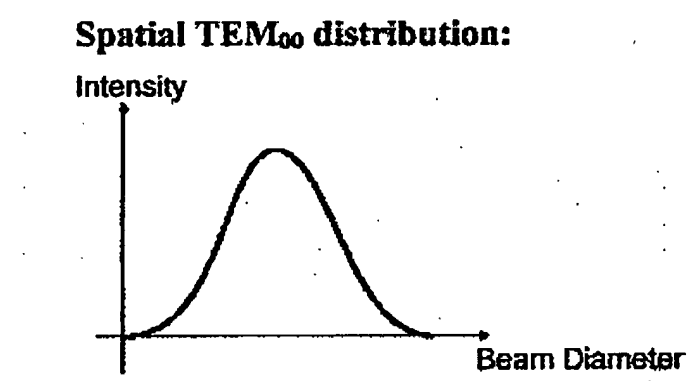
Clarke discloses low resolution Raman spectroscopic systems and methods for in-vivo detection and analysis of a lesion in a lumen of a subject. The system uses a multi-mode laser attached to a catheter in making in-vivo Raman spectroscopic measurements of the lumen. The system includes a light collector and/or a light dispersion element as well as a detector to measure spectral patterns that indicate the presence of the lesion. Based on the spectral response of the lumen, the presence (or absence) of a lesion is determined. In addition, the components of the lesion can also be identified based on the unique Raman spectrum associated with each component.

Col. 3, lines 11-23 of Clarke make it clear that the excitation source disclosed is a narrowband source, such as the 785 nm GaAs laser diode noted below.

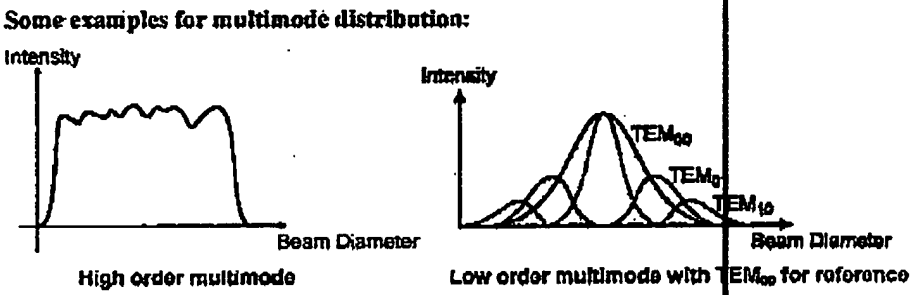
According to some features of the present invention, the multi-mode laser element produces laser radiation having a wavelength between about 700 nanometers (nm) and about 2.4 micrometers (μM), more preferably between 700 nm and about 1.1 .mu.M. Preferably, the multi-mode laser produces radiation having a line width of at least 2 nm.

The multi-mode laser preferably has a power between about 50 milliwatts (mW) and about 1000 mW, and more preferably, greater than about 150 mW in some applications. One example of a multi-mode laser element for use with the present invention is a 785 nm GaAs laser diode. This GaAs multi-mode laser has a spectral distribution FWHM of approximately 30 cm.

The multi-mode aspect of Clarke's excitation source relates to the cross sectional shape of the laser beam along the beam diameter, and has essentially nothing to do with the broadband or narrowband nature of the radiation source. In contrast to a single mode beam which is has a Gaussian shaped cross sectional beam intensity, for lasers with a high order multimode structure, the cross sectional intensity of the beam can be almost rectangular (see below).



Single mode



Besides lacking the required a broadband excitation source, the system disclosed by Clarke also lacks a structure for scanning the excitation wavelength, such as Applicant's AOTF. See Col. 4, lines 41 -51 of Clarke which discloses "The lesion produces Raman scattered radiation that is collected by a collection fiber bundle 8, through which the radiation travels to a low resolution dispersion element 9, that serves to disperse the scattered light into its different wavelength components, that are detected by a detection array 10, and analyzed by a microprocessor 11". Accordingly, Clarke discloses the use of a narrowband excitation source. Accordingly, synchronous scanning is not possible because a broadband source is required (as well as a structure for scanning the excitation beam which is also absent in Clarke).

Moreover, the emission wavelength is not scanned by Clarke as made clear by col. 4, lines 61-67 (copied below).

Raman scattered radiation from the lesion 14, is collected by an optical waveguide and is transmitted back into the catheter. The scattered radiation is collected by the fiber bundle 8, which may optionally have a notched filter 21. The scattered radiation is dispersed into various components by the dispersion element, and detected by the detective array 10.

Returning now to the Examiner's assertions regarding Clarke, Col. 2 lines 27-63 (copied below) was cited by the Examiner to support the assertion that Clarke discloses "synchronous scanning a wavelength of excitation emission radiations":

Accordingly, in one aspect, the present invention provides a system for detecting the presence of a lesion in the lumen of a subject using low resolution Raman spectroscopy. The system can include a catheter comprising an excitation fiber through which multi-mode radiation can propagate to irradiate a target region of a lumen,

a multi-mode laser for irradiating the target region to produce a Raman spectrum consisting of scattered electromagnetic radiation,

a low resolution dispersion element positioned to receive and separate the scattered radiation into different wavelength components,

a detection array, optically aligned with the dispersion element for detecting at least some of the wavelength components of the scattered light, and

a processor for processing data from the detector array.

In use, the multi-mode laser irradiates the target to produce a Raman spectrum. The Raman spectrum is composed of scattered electromagnetic radiation characterized by a particular distribution of wavelengths. The Raman spectrum is a result of the scattering of the laser radiation as it interacts with the target.

The collector element collects the radiation scattered from the target. The collection element can be an optical fiber. The collection fiber can have a first end positioned for collecting scattered radiation, and a second end positioned in selected proximity to the dispersion element. One or more filters can also be employed in the systems of the present invention to reduce or attenuate optical "noise". For example, a notch filter can be coupled to the first end of the collection fiber for filtering the excitation source background.

The dispersion element distributes the scattered radiation into different wavelength components. The detection array detects the scattered radiation in different wavelength ranges, and a processor processes the detected array data to detect the presence and/or the components of the lesion.

The only description regarding the excitation source above is that it is a "multi-mode laser". As noted earlier by Applicant, a multi-mode laser only refers to the non-Gaussian shaped cross sectional beam intensity (e.g. rectangular). Accordingly, in the above passage Clarke does not disclose or suggest the "synchronous scanning" recited in method claim 1 or the implicitly asserted "structure for synchronously scanning a wavelength of said excitation" recited in system claim 15.

Col. 6, lines 35-55 were also cited by the Examiner:

FIG. 2 shows one embodiment of the invention. FIG. 2 is an apparatus for spectroscopic analysis that includes a casing or sheath 15, an excitation fiber 3, through which radiation can be transmitted and emitted as a conical pattern of excitation radiation 4. The apparatus further includes a number of fibers 16, which receive Raman scattered radiation 17, from the surrounding lumen. Although illustrated as optical fibers, it should be apparent that means can be any light waveguide or assembly of optical elements known in the art, for collection of radiation form the lumen.

FIG. 2A is a cross sectional view of the apparatus shown in FIG. 2, illustrating the relative positions of the excitation fiber 3, and the collections fibers 16, as well as the protective sheath 15.

FIG. 3 is an apparatus for spectroscopic analysis which includes a catheter 5, that has an excitation fiber 3, and collection fibers 16, surrounded by a sheath 15. The catheter 5, also includes a light directing element 6, which directs multi-mode laser radiation in a sideways direction to produce directed light 7, used to irradiate a lesion in the lumen.

There is no scanning of the excitation or emission wavelength disclosed or suggested in the above excerpt. Accordingly, in the above passage Clarke does not disclose or suggest the "synchronous scanning" recited in method claim 1 or the implicitly asserted "structure for synchronously scanning a wavelength of said excitation" recited in system claim 15.

Col. 8, lines 10-32 of Clark (copied below) was also cited by the Examiner for "synchronous scanning":

As an indicator of in-vivo analysis using low resonance Raman spectroscopy, the following figures indicate the changes envisioned between a normal artery, an artery with a fibrous plaque and an artery with a calcified plague.

FIG. 5A is a graph of intensity in arbitrary units versus Raman shift wavelength for a normal arterial lumen. The graph shows triglyceride and protein features at approximately 1650, 1250 and 1450 cm.sup.-1 Raman shifts. This is typical of arterial walls which are composed of protein fibers and smooth muscle cells.

FIG. 5B is a graph of intensity in arbitrary units versus Raman shift wavelength for a fibrous atherosclerotic plaque. It is known that plaques that are not calcified produce a different Raman spectra than those that are calcified. The graph displays spectral features from the sterol rings of free cholesterol and cholesterol esters, characteristic of lipid laden foam cells.

FIG. 5C is a graph of intensity in arbitrary units versus Raman shift wavelength for a calcified atherosclerotic plaque. The graph shows a distinguishable peak of a phosphate band at 960 cm.sup.-1, which is characteristic of calcium salts.

The Raman data shown in Fig. 5A-C is simply "composed of scattered electromagnetic radiation characterized by a particular distribution of wavelengths. The

Raman spectrum is a result of the scattering of the laser radiation as it interacts with the target" (col. 2 lines 45-49). There is no scanning of the excitation or emission wavelength disclosed or suggested in the above excerpt or Raman data shown. Accordingly, in the above passage Clarke does not disclose or suggest the "synchronous scanning" recited in method claim 1 or the implicitly asserted "structure for synchronously scanning a wavelength of said excitation" recited in system claim 15.

The other reference cited against the claims, Boppart, does not disclose or suggest synchronous scanning either. Accordingly, method claim 1, system claim 15 and their respective dependent claims are patentable over the cited art.

Several of Applicant's dependent claims recite independently patentable limitations. For example, claim 11 recites "said synchronous scanning step comprises directing broadband excitation radiation into a first acousto-optic tunable filter (AOTF), and varying an input radio frequency to said first filter to achieve a range of wavelengths of said excitation radiation". However, the Examiner rejected claim 11 et al. based on the following assertion:

> **Claims 11-13, 21, and 22: Clarke discloses that the excitation radiation causes scattering in emission radiation therefore, optical filter is essential to rid of unwanted radiation (column 4, lines 61-67).**

The "optical filter" referenced by the Examiner above is "notched filter 21". A notched filter is synonymous with a band-stop filter and is used in optics to reject an unwanted band of radiation. In contrast, Applicant's claimed AOTF is an acousto-optic tunable filter (AOTF). In AOTFs a piezoelectric transducer is bonded to a birefringent crystal (typically TeO_2 or quartz). The transducer is excited by a radio frequency (RF)

signal at 50-200 MHz and generates acoustic waves in a birefringent crystal which provides the tuning which allows the wavelength passed to be scanned. A notch filter is not a tunable filter, nor is it clearly the claimed AOTF.

Accordingly, claims 11-13, 21 and 22 which recite an AOTF provide a separate basis for patentability.

Claim 6 recites "said excitation radiation is an intensity-modulated electromagnetic excitation signal, further comprising the step of determining at least one lifetime from said sample". Claims 5-10, 14, 16-20, and 23-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Clarke as applied to claims 1 and 15 above, and further in view of Boppart et al. (US 6,485,413). According to the Examiner:

Claims 6-9 and 16-20: In addition, Boppart et al further disclose back end processing where the radiation's intensity is modulates and the time resolved spectroscopy or phase correction is achieved (column 5, lines 3-25; column 7, line 63 - column 8, line 18).

Applicant respectfully disagrees with the above assertions. Boppart discloses an imaging system for performing forward scanning imaging for application to therapeutic and diagnostic devises used in medical procedures. The imaging system includes forward directed optical coherence tomography (OCT), and non-retroreflected forward scanning OCT. Also interferometric imaging and ranging techniques and fluorescent, Raman, two-photon, and diffuse wave imaging can be used.

Col. 5, lines 3-25 and col. 7, line 63 to col. 8 line 18 is copied below:

Three basic types of OCT imaging engines are known in the art and include: reference-arm scanning, frequency tunable optical source, and optical spectral analysis imaging. In each of these embodiments the interferometer 19 and associated optics are used to couple light from the optical source onto the sample and optical reference. The interferometer 19 also couples light after being altered by the sample and optical reference (either delayed, transmitted, reflected, or scattered) onto the receiver processing unit 38 in such a way that optical interference between the sample and reference light

occurs and is detected and converted to electronic signal(s). The interferometer may contain free-space optics and/or optical fibers. In one embodiment the fibers are single-mode fibers. The interferometer may be of a variety of embodiments including Michelson or Mach-Zehnder configurations. Within the interferometer frequency or phase modulation elements enable en face imaging or enhanced signal processing; dispersion balancing and compensation elements maintain high longitudinal resolution; and polarization controllers, polarization-maintaining or single-polarization fiber, or polarization diversity techniques maintain good signal-to-noise ratio or provide information concerning the birefringence of the sample.

Although much of the discussion in this section has focused on OCT imaging engine embodiments, a variety of other optical imaging engines can be used with the scanning and probe modules described in this invention. These include: transillumination techniques, diffuse-wave imaging techniques, confocal microscopy, and various types of fluorescence discrimination and imaging techniques. Diffuse-wave imaging is a fairly new optical imaging technology that uses the diffusion properties of highly scattered light to perform imaging. Diffuse-wave imaging has demonstrated clinical applications for functional monitoring such as for the determination of oxygenation. An interferometer is not required for diffuse-wave imaging. The source is often a sinusoidally intensity modulated laser and the receiver is a direct detection receiver that measures the relative intensity and phase of the detected light with respect to the transmitted light. The delivery system need not be a single-mode fiber and often a multi-mode fiber offers superior signal collection. Images of the specimens' optical properties can be obtained by plotting the phase or magnitude of the detected optical intensity as a function of scan location. As with the OCT imaging engine, the images are displayed and used for diagnosis or in guiding therapeutic procedures.

Although Boppart discloses use of intensity modulated radiation, the intensity modulated radiation is used to improve interferometric imaging (the basis of OCT), not for Applicant's claimed "step of determining at least one lifetime from said sample" (Claim 6). Moreover, claim 7 recites "said intensity-modulated electromagnetic excitation signal comprises at least one radiation pulse, said radiation pulse having a pulse width shorter than said lifetime, wherein said lifetime is determined using time resolved spectroscopy". Boppart does not disclose or suggest the intensity-modulated electromagnetic excitation signal comprises at least one radiation pulse, nor said radiation pulse having a pulse width shorter than said lifetime, nor determining the d lifetime using time resolved spectroscopy.

Applicant has made every effort to present claims which distinguish over the cited art, and it is believed that all pending claims are in condition for allowance. However, Applicant requests the Examiner to call the undersigned (direct dial 561-671-3662) after review of this Reply if the Examiner determines that any clarification is necessary to permit issuance of a Notice of Allowance. If any fee other than the fees for one-month extension is due, the Commissioner for Patents is hereby authorized to charge any deficiency in fees due or credit an excess in fees with the filing of the papers submitted herein during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,

Date: 2/3/06

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